# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
EDWIN V. MERKEL
NIXON PEABODY LLP
CLINTON SQUARE, P.O. BOX 31051
ROCHESTER, NY 14603-1051

REC'D 28 JUL 2006
PCT
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## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

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|---|---|
| Date of mailing (*day/month/year*) | 25 JUL 2006 |
| Applicant's or agent's file reference: 176/61751 | FOR FURTHER ACTION: See paragraph 2 below |

| International application No. | International filing date (*day/month/year*) | Priority date (*day/month/year*) |
|---|---|---|
| PCT/US05/00053 | 03 January 2005 (03.01.2005) | 02 January 2004 (02.01.2004) |

International Patent Classification (IPC) or both national classification and IPC

IPC: C12Q 1/68( 2006.01);C07H 21/02( 2006.01),21/04( 2006.01)
USPC: 435/6;536/23.1,24.3

Applicant

UNIVERSITY OF ROCHESTER

1. This opinion contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/ US | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (571) 273-3201 | 08 July 2006 (08.07.2006) | Ethan Whisenant, Ph.D.<br>Telephone No. (571) 272-1600 |

Form PCT/ISA/237 (cover sheet) (April 2005)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/00053

**Box No. I Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/00053

**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims 1-17 | YES |
| | Claims 18-30 | NO |
| Inventive step (IS) | Claims NONE | YES |
| | Claims 1-30 | NO |
| Industrial applicability (IA) | Claims 1-30 | YES |
| | Claims NONE | NO |

2. Citations and explanations:

Please See Continuation Sheet

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US05/00053

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claim 1 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 1 is indefinite for the following reason(s): Claims 1 is indefinite because there is no nexus between the preamble and the claim steps. Claim 1 in its preamble direct to a method which is to accomplish a particular goal. However, none of the claim steps states that this goal is accomplished. For clarity, claimed methods should recite that the purpose of the method has been attained (i.e. provide a nexus between the preamble and the claim steps).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

1. Claims 18-21, 24 and 27-30 lack novelty under PCT Article 33(2) as being anticipated by Bonnet et al. [PNAS 96: 6171-6176 (1999].

Bonnet et al. teach in isolated nucleic acid molecule comprising all of the structural limitations recited in claims 18-21, 24 and 27-30.

2. Claims 18-22 and 24-30 lack novelty under PCT Article 33(2) as being anticipated by Bu et al. [J. Am. Chem. Soc. 125: 4012-4013 (2003)].

Du et al. teach an isolated nucleic acid molecule comprising all of the structural limitations recited in claims 18-22 and 24-30.

3. Claims 18-21 and 23-30 lack novelty under PCT Article 33(2) as being anticipated by Dubertret et al. [Nature Biotech. 19: 365-370 (2001)].

Dubertret et al. teach an isolated nucleic acid molecule comprising all of the structural limitations recited in claims 18-21 and 23-30.

4. Claims 1-11, 14, 17-21, 24 and 27-30 lack an inventive step under PCT Article 33(3) as being obvious over Neri et al. [U.S 6,355,437 (2002)] in view of Bonnet et al. [PNAS 96: 6171-6176 (1999)].

Neri et al. teach a method of identifying nucleic acid probes for a target nucleic acid sequence comprising a folded structure. Neri et al. does not teach hairpin probes, however, Bonnet et al. do teach hairpin nucleic acid probes. Therefore, absent an unexpected result it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to substitute the hairpin probes of Bonnet et al. for the linear probes taught by Neri et al. The ordinary artisan would have been motivated to make the modification recited above in order to gain the advantages of probes comprising hairpin structure i.e. higher specificity, see at least for example, the abstract of Bonnet et al. Furthermore, please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been prima facie obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results

Supplemental Box
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when combined for the common known purpose. As regards the limitations recited in claims 6-7 please note that it was well known at the time of the invention to perform nucleic acid database searches in order to identify nucleotide sequences similar to an intended target nucleic acid. Such information would have been useful in determining the likelihood of cross reactivity with non target nucleic acid in a hybridization assay.

5. Claims 12, 15-16, 22 and 25-26 lack an inventive step under PCT Article 33(3) as being obvious over Neri et al [US 6,355,437 (2002)] in view of Bonnet et al. [PNAS 96:6171-6176 (1999)] as applied against claims 1, 8 and 19 above and further in view of Du et al. [J. Am. Chem. Soc. 125: 4012-4013 (2003)].

Neri et al. in view of Bonnet et al. teach a method of preparing a molecular beacon comprising all of the limitations recited in claim 12 except these authors do not teach an embodiment wherein the quenching agent is a solid surface. However, Du et al. do teach a molecular beacon probe wherein the quenching agent is a solid surface. Therefore, absent an unexpected result it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to substitute the hairpin probes of Du et al. for the hairpin probes reasonably suggested by the combination of Neri et al. in view of Bonnet et al. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been prima facie obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

6. Claims 13, 15-16, 23 and 25-26 lack an inventive step under PCT Article 33(3) as being obvious over Neri et al. [US 6,355,437 (2002)] in view of Bonnet et al. [PNAS 96 : 6171-6176 (1999)] as applied against claims 1 and 8 above and further in view of Dubertret et al. [Nature Biotech. 19: 365-370 (2001)].

Neri et al. in view of Bonnet et al. teach a method of preparing a molecular beacon comprising all of the limitations recited in claim 12 except these authors do not teach an embodiment wherein the quenching agent is a micro- or a nano-particle. However, Dubertret et al. do teach a molecular beacon probe wherein the quenching agent is a micro- or a nano-particle. Therefore, absent t an unexpected result it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to substitute the hairpin probes of Dubertret et al. for the hairpin probes reasonably suggested by the combination of Neri et al. in view of Bonnet et al. Please note that the substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been prima facie obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

7. Claims 1-30 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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7. Claims 1-30 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.